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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,916	10/02/2000	Carl Anthony Blau	UOFW115624	4343

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/582,916	BLAU ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,12-19,21,24,25,32-39,41,42,56,57,59 and 89-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-5, 12-19, 21, 24-25, 32-39, 41-42, 56-57, 59, and 89-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/08 has been entered. As requested, applicant's amendment and response received on 3/26/08, previously non-entered, have been entered. Claims 2-3, 6-11, 20, 22-23, 26-31, 40, 43-55, 58, and 60-88 have been canceled and new claims 89-91 have been added. Please note that the amendment incorrectly numbers the new claims as 60-62. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claims 60-62 have therefore been renumbered as 89-91. Therefore, claims 1, 4-5, 12-19, 21, 24-25, 32-39, 41-42, 56-57, 59, and 89-91 are now pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Objections

The objection to claims 3, 23, and 45 is withdrawn in view of the cancellation of these claims.

Claim Rejections - 35 USC § 112

Applicant's amendment has necessitated the following new rejection of the claims under 35 U.S.C. 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5, 12-19, 21, 24-25, 32-39, 41-42, 56-57, 59, and 89-91 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) as amended contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. In amended cases, subject matter not disclosed in the original application is sometimes added and a claim directed thereto. Such a claim is rejected on the ground that it recites elements without support in the original disclosure under 35 USC 112, first

paragraph, *Waldemar Link, GmbH & Co. v. Osteonics Corp.* 32 F.3d 556, 559, 31 USPQ2d 1855, 1857 (Fed. Cir. 1994); *In re Rasmussen,* 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

Applicant has amended the claims to recite a specific chemical structure for the divalent ligand. The chemical formula represents a genus of molecules. The size of the genus appears to be large, encompassing numerous species as represented by the various R, R', G, G', X, and X' groups in the structure. However, the chemical formula now claimed is not disclosed in the specification. Further, as R, R', G, G', X, X' etc. have not been defined in the specification, the exact size of the claimed genus cannot be determined. The specification generally teaches the use of a ligand capable of dimerizing two molecules which is a dimerizing agent/drug for fusion molecules comprising the drug binding protein domain. The specification lists a number of preferred drug binding protein domains including FKBP on page 5. The dimerizer/drug is described as being preferably a non-proteinaceous molecule which is cell permeant and has a molecular weight of about 5kD (see the specification on page 7). None of the generic disclosure teaches or suggests the specific chemical structure now claimed. Regarding dimerizers/drugs capable of binding to the FKBP derivative F36V, the specification only discloses 3 specific species, AP1510, AP1903, and AP20187. On page 36, the specification provides the chemical structure of AP1510. The structures of AP1903 and AP20187 are not provided. While the structure of AP1510 appears to represent one species of the much larger genus of molecules encompassed by the chemical structure recited in the claims, the disclosure of a single species does not establish conception or possession of the now claimed genus of molecules. Assuming arguendo that AP1903 and AP20187 have chemical structures that also fit within the claimed structure, the size of the genus claimed is such that disclosure of one or three species is not

sufficient to show that the inventors had actually contemplated and had in their possession the claimed genus of chemical compounds capable of binding to F36V at the time of filing. It is further noted that the genus of drugs/dimerizers generically disclosed in the specification, and discussed above, also does not demonstrate possession of the particular sub-genus now claimed. Case law states, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Also, "[w]hatever may be the viability of an inductive-deductive approach to arriving at a claimed subgenus, it cannot be said that such a subgenus is necessarily described by a genus encompassing it and a species upon which it reads." (emphasis added) *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). See also *In re Wilder*, 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984), and *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971).

Therefore, while the specification provides adequate written description for AP1510, AP1903, and AP20187, the specification does not provide adequate written description for the genus of molecules encompassed by the chemical structure now claimed. As such, the newly added chemical structure constitutes new matter

The rejection of claims 3, 23, and 45 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the cancellation of these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-5, 12-19, 21, 24-25, 32-39, 41-42, 56-57, 59, and 89-91 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The independent claims have been amended to recite a divalent ligand having a specific chemical formula which includes at particular molecule positions within the structure the characters X, X', G, G', R, and R', which are typically included to denote alternate elements or chemical structures available for each specified location within the molecule. However, as discussed in detail above, the claimed chemical formula is not disclosed in the specification. Further, the specification does not disclose or define the X, X', G, G', R, and R' groups. As such, the metes and bounds of the claimed divalent ligand recited in claims 1, 4-5, 12-19, 21, 24-25, 32-39, 41-42, 56-57, 59, and 89-91 cannot be determined.

Claim 21 is further indefinite in that it lacks antecedent basis for “said transduced cells”.

Claim 24 is further indefinite in that it lacks antecedent basis for "the population". Claim 21 refers to a "subpopulation".

Claim 32 is further indefinite in that it depends on claim 21, and refers to “the transduction thereof with the retroviral vector..”. However, claim 21 contains a step of “providing a subpopulation of mammalian primary hematopoietic stem cells which contain a retroviral vector…”. Claim 21 does not recite a step for transducing the cell. Thus, there is no antecedent basis for transducing cells in claim 32. The claim is also indefinite as it is unclear whether the applicant is intending to add the step of transducing cells to the method of claim 21.

Claim 39 is further indefinite in that it depends on claim 21, and adds the limitation, "wherein the cells are transduced within the mammal". However, claim 21 does not contain a step of transducing cells. As such, claim 39 lacks antecedent basis and is indefinite.

Claim 56 is further indefinite in that it recites a method of using the product of either claim 4 or 24. Specifically, claim 56 refers to "the bone marrow cell, cord blood cell, or peripheral blood cell of claim 4 or 24". However, claims 4 and 24 are drawn to populations of primary hematopoietic cells comprising bone marrow cells, cord blood cells or peripheral blood cells, not to bone marrow cells, cord blood cells or peripheral blood cells themselves. As such, the claim is confusing and indefinite.

Claim Rejections - 35 USC § 103

The rejection of claims 1-42, 59-66, and 70-76 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., in view of Spencer et al. (1996) Current Biology, Vol. 6 (7), 839-847 and Blau et al. (1996) Blood, Vol. 88 (10 Suppl. 1 part 1-2), p542A, meeting abstract, hereafter referred to as Blau (1996), is withdrawn in view of applicant's amendments to the claims.

The rejection of claims 44-53, and 55-58 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., in view of U.S. 5,994,313 (11/30/99), hereafter referred to as Crabtree et al., Spencer et al. (1996) Current Biology, Vol. 6 (7), 839-847, and Blau et al. (1996) Blood, Vol. 88 (10 Suppl. 1 part 1-2),

p542A, meeting abstract, hereafter referred to as Blau (1996), is withdrawn in view of applicant's amendments to the claims.

Applicant's amendments to the claims have necessitated the following new grounds of rejection of the claims under 35 U.S.C. 103(a).

Claims 1, 4-5, 12-19, 21, 24-25, 32-39, 41-42, 56-57, 59, and 89-91 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., in view of Blau et al. (1996) Blood, Vol. 88 (10 Suppl. 1 part 1-2), p542A, meeting abstract, hereafter referred to as Blau (1996), Ramsfjell et al. (1996) Blood, Vol. 88 (12), 4481-4492, and U.S. Patent No. 6,150,527 (2000), hereafter referred to as Holt et al.

Capon et al. teaches the transduction of cells with a recombinant nucleic acid encoding 1) a chimeric protein comprising an extracellular inducer-responsive clustering domain capable of binding an extracellular inducer that transmits a signal to a proliferation signaling domain, a transmembrane domain, and a proliferation domain that signals a host cell to divide, or 2) a chimeric protein comprising an intracellular inducer-responsive clustering domain capable of binding an intracellular that transmits a signal to a proliferation signaling domain and a proliferation domain that signals a host cell to divide (abstract, and columns 1-2). In particular, Capon et al. teaches that the extracellular or intracellular inducer-responsive clustering domain (ICD) of the chimeric protein is derived from immunophilin, e.g. FKBP, and that the cytoplasmic signal transduction domain is derived from homodimerizing receptors such as TPOR

(thrombopoietin receptor or mpl) (Capon et al., columns 7, 9, 13, 15, 34-35, and 42-43). Capon et al. further teaches that cells transduced with an appropriate vector comprising the nucleic acid, such as a retroviral vector, which encodes said chimeric protein can be induced to expand and proliferate by exposing the cells to a multivalent inducer molecule (Capon et al., columns 19 and 21+). In the case of chimeric proteins which encode FKBP, Capon et al. teaches that the inducer molecule is a multivalent cell-permeant drug with a molecule weight of less than 5 kD such as FK1012 (Capon et al., columns 15, 19, 21 and 22). In addition, Capon et al. teaches that target cells for expansion can be transduced *in vitro* or *in vivo* for use in the treatment of human diseases such as cancer or autoimmune disease (Capon et al., columns 1, 16 and 21-22). In regards to cells transduced *ex vivo* and introduced into the host mammal, Capon et al. teaches that the cells can be allogeneic or autologous cells, including hematopoietic stem cells capable of developing into cells of the myeloid and lymphoid lineages (Capon et al., columns 16, and 21-22).

As noted above, Capon et al. discloses that FKBP can be used as an ICD, TPOR (thrombopoietin receptor,mpl) can be used as a cytoplasmic signal transduction domain, and that the chimeric proteins can be expressed in hematopoietic stem cells. However, Capon et al. does not specifically exemplify ligand induced proliferation of hematopoietic stem cells expressing a chimeric protein comprising FKBP and TPOR. Blau et al. (1996) supplements Capon et al. by teaching that cell proliferation of hematopoietic stem cells can be effectively induced through dimerization of chimeric receptors comprising FKBP and EpoR using FK1012 (Blau et al., abstract). Ramsfjell et al. further supplements Capon et al and Blau et al. by teaching that TPOR is normally expressed in primitive hematopoietic stem cells and signaling through the TPOR

induces the proliferation of hematopoietic stem cells both *in vivo* and *in vitro* (Ramsfjell et al., page 4481). Therefore, by demonstrating that chimeric proteins comprising FKBP as the ICD and a growth factor receptor as the cytoplasmic signal transduction domain can be used to induce hematopoietic stem cell proliferation, and by teaching that the growth factor receptor TPOR is naturally expressed on hematopoietic stem cells and can induce cell proliferation, the prior art at the time of filing provides a reasonable expectation of success that the particular species of chimeric fusion protein comprising FKBP and TPOR disclosed by Capon et al. could effectively induce cell proliferation following ligand induced dimerization.

Capon et al. differs from the instant invention by not teaching an FKBP that has the mutation F36V, or the use of a multivalent inducer ligand capable of dimerizing F36V binding domains such as AP1503. However, Capon et al. does suggest that modifications can be made to the ICD to create improved receptor-ligand binding (Capon et al., column 5, lines 12-15). Further, at the time of filing, various modifications to FKBPs were known which increased their affinity or selectivity for their ligand. Holt et al. supplements Capon et al. by teaching various synthetic FKBP dimerizing ligands such as AP1903 with improved properties compared to FK1012 and that bind to a modified FKBP with an F36V mutation (Holt et al., column 43, 125-126, 152). Specifically, Holt et al. teaches that FKBP domains have been used in fusion proteins comprising a ligand binding domain and an effector molecule where multimerization of the ligand binding domains in these fusion proteins triggers a desired physiological event such as cell death or cell proliferation (Holt et al., column 2, 75). Holt et al. teaches that the commonly used FKBP dimerizer FK1012 is large, complex and inconvenient to produce compared to smaller synthetic molecules such as AP1903 (Holt et al., column 1). Holt et al. further teaches

that AP1903 has high binding affinity for F36V (Holt et al., column 43). Holt et al. further teaches effective doses of the dimerizing ligands for both *ex vivo* and *in vivo* dimerization of fusion proteins (Holt et al., column 81, and 150-152).

Therefore, based on the motivation to make modifications to the ICD to create improved receptor-ligand binding provided by Capon et al., the teachings of Holt et al. that synthetic ligands such as AP1903 are more convenient to produce and have increased affinity, and motivation provided by Holt et al. for using modified FKBP domains such as F36V and synthetic dimerizing ligands such as AP1903 in methods of triggering biological events such as cell proliferation using fusion proteins comprising a modified FKBP and an effector, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the modified F36V binding domain taught by Holt et al. as the ICD in the chimeric proteins taught by Capon et al. and further to use the synthetic dimerizing ligand AP1903 instead of FK1012 to trigger cell proliferation and differentiation of hematopoietic stem cells expressing the chimeric protein. In addition, based on the high degree of skill in the art of molecular biology at the time of filing, and the specific guidance provided by Capon et al. and Holt et al., the skilled artisan would have had a reasonable expectation of success in making a retroviral expression vector encoding a chimeric protein comprising F36V and a proliferation signaling domain such as the thrombopoietin receptor (mpl) signaling domain TPOR and in using those vectors to transfect/transduce hematopoietic stem cells according to Capon et al. Further, as discussed above, the state of the art as represented by Blau et al. and Ramsfjell et al. provides a reasonable expectation that dimerization of chimeric proteins comprising an FKBP binding domain and a

TPOR cytoplasmic signal transduction domain on hematopoietic stem cells would result in cell proliferation.

Applicant's arguments have been considered as they apply to the new grounds of rejection of the claims presented above. However, applicant's arguments have not been found persuasive in overcoming the instant grounds of rejection under 103. It is first noted that arguments regarding the teachings of Crabtree et al. and Spencer et al. are moot as these references are no longer part of the 103 rejection. Further, arguments that the particular limitations of F36V and divalent ligands of the claimed chemical formula are not taught by any of the previously cited references are not persuasive as the instant rejection cites Holt et al. which not only teaches the particular use of F36V in chimeric proteins comprising signal transduction domains and further the dimerization of such F36V containing chimeric proteins using ligands according to the instantly claimed chemical formula including AP1903. Turning to applicant's arguments regarding Capon et al., the applicant now argues that Capon et al. at best presents various lists of ICDs, signaling domains, dimerizing ligands, and cells such that there would be no motivation or reasonable expectation of success in making or using the specific combination of a chimeric protein comprising FKBP and TPOR in hematopoietic stem cells as claimed. In response, while the disclosure of Capon, like that of the instant specification, recites numerous functional equivalents for the ICD and signaling portions of the chimeric protein, motivation and a reasonable expectation of success in making and using the specific FKBP/TPOR chimeric protein species claimed is provided by the teachings of Blau et al. and Ramsfjell et al. As discussed in the rejection above, Blau et al. specifically teaches hematopoietic

stem cells modified to express a chimeric protein comprising FKBP and EPOR and demonstrates that dimerization of the FKBP domains with FK1012 induces cell proliferation. Ramsfjell et al. further teaches that unlike EPOR, TPOR is actually expressed in primitive hematopoietic stem cells and that signaling through TPOR induces hematopoietic stem cell proliferation. Thus, the skilled artisan would have been motivated to make and use the particular species of FKBP/TPOR chimeric protein encompassed by the disclosure of Capon et al. to induce hematopoietic stem cell proliferation with a reasonable expectation of success. Finally, regarding Blau et al. and the predictability of inducing cell proliferation of primary versus cell line hematopoietic stem cells, while Blau et al. may have utilized a cell line rather than a primary hematopoietic stem cell, Ramsfjell et al. teaches that TPOR is not only naturally expressed in hematopoietic stem cells but that signaling through TPOR triggers cell proliferation. Thus, despite the "caution" in interpreting the results from established cell lines referred to by applicant as suggested by Lewin (evidence newly submitted by applicant with the after-final response of 3/26/08), the skilled artisan would have reasonably expected based on the natural function of TPOR in primary hematopoietic stem cells as taught by Ramsfjell et al. that dimer induced signaling through TPOR would in fact result in hematopoietic stem cell proliferation.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all

official communications, the new technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633